REMARKS

Please amend the attorney docket number to 09172.0006U1.

Originally filed claims 1-38 are subject to a restriction requirement. New claims 39-75 have been added herein. Therefore, claims 1-75 are pending.

Specification Amendments

The text at page 26, lines 15-17, has been amended herein to disclose:

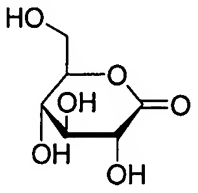
> "Halogen" is intended to mean a fluorine, chlorine, or bromine atom or ion or group. Preferred halogens are chlorine and bromine. The most preferred is chlorine. In certain embodiments, it is understood that a sulfur-containing group (*e.g.*, a thiol group or a sulfonyl group) can be used in place of a halogen.

Those of ordinary skill in organic chemistry understand that halogens include fluorine, chlorine, and bromine atoms, ions, or groups, as originally recited in the claim, but might misinterpret the meaning of other portions of the original specification definition of halogen on specification page 26. One of ordinary skill in the art would interpret that sulfur atoms, thiol groups, or sulfonyl groups that are aspects of the invention are not literally "halogens" but can function as chemical equivalents of "halogens." Accordingly, Applicants request correction of the original specification definition to clarify that Applicants do not contend that sulfur atoms, thiol groups, or sulfonyl groups are not literally halogens, but can be used in place of halogens.

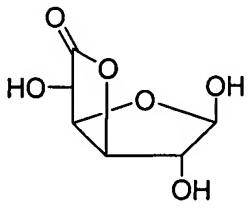
Schemes 1, 2, and 3 which are part of Examples 1, 2, and 3 on pages 46 and 47 have been amended to correct certain errors in those drawings. The textual descriptions of Examples 1, 2, and 3 were and are completely correct, but the corresponding drawings contain errors, and Applicants believe clarification and/or correction of the errors in the drawings is in the interest of the public.

First, the text of Example 1 correctly describes the reaction of gluconolactone with 3-hydroxytyramine, to produce dopamine gluconamide, but the corresponding drawing in Scheme 1 contains two obvious errors. Those of ordinary skill in the art are well aware, as evidenced as by THE MERCK INDEX: AN ENCYCLOPEDIA OF CHEMICALS, DRUGS, AND BIOLOGICALS,

THIRTEENTH EDITION 4471 (Maryadele J. O'Neil et al. eds., 2001; copy attached hereto as Exhibit A) that the chemical structure of gluconolactone is the 6-carbon monocyclic structure shown below on the left, rather than the 6-carbon bicyclic lactone structure shown in original Scheme 1.



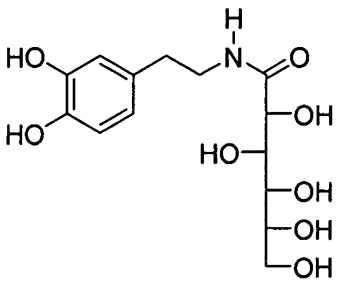
Gluconolactone



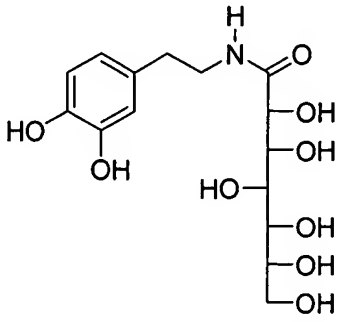
Incorrect Bicyclic Starting Material shown in original Scheme 1

The inclusion of the drawing of the 6-carbon bicyclic lactone structure included in original Scheme 1 is simply and obviously erroneous. Clarification /correction of this error, is obvious to those of ordinary skill in the art, and consistent with the correct verbal text of Example 1, is in the interests of the public, and Applicants request entry of the amendments to Scheme 1 in order to correct this obvious error.

Moreover, there is a second obvious error in Scheme 1, namely the drawing of the dopamine gluconamide product, erroneously shows a straight chain sugar residue having 7 carbons, rather than the six carbon sugar residue actually present in dopamine gluconamide. The same error is repeated in Scheme 2.



Dopamine Gluconamide
Illustrated with correct 6 carbon sugar residue

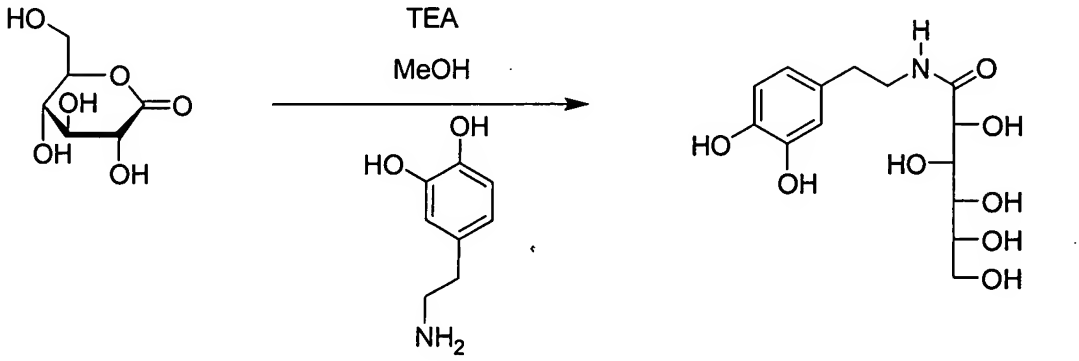


Erroneous Drawing of Schemes 1 (and 2)
Showing erroneous 7 carbon sugar residue

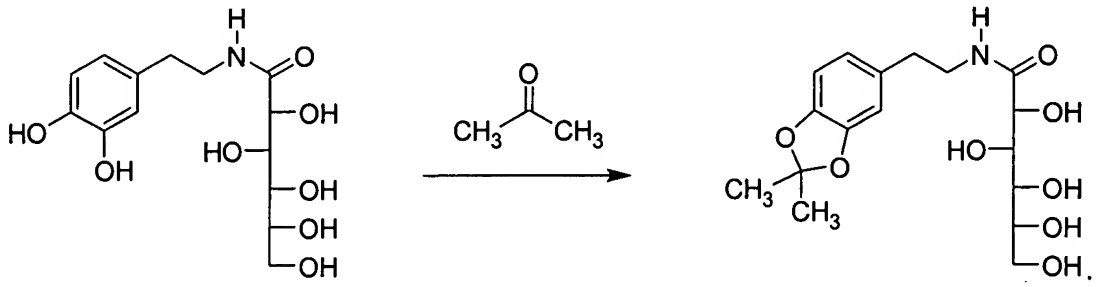
The subsequent drawings of compounds having sugar residues derived from glucose in Schemes 1, 2, and 3 all repeat the same error of including an erroneous 7th carbon atom in the sugar residue. Applicants have corrected all these drawings to remove the carbon atom (and associated hydroxyl group) just below the carbonyl carbon, while retaining all other features, including the relative stereochemistries of the hydroxyl substituents.

One of ordinary skill in art would readily recognize these obvious errors. One of ordinary skill in the art would expect a "glucono" sugar residue (ultimately derived from glucose) to have six carbons, rather than seven carbons. Moreover, the simple ring opening reactions of a lactone (such as gluconolactone) with an amine (such 3-hydroxytriptamine) is well known to result in amides, and the amide would be expected to retain the number of carbon atoms possessed by the original lactone and amine, and would not be expected to ordinarily result in the gain or loss of carbon atoms, as is implied in original Scheme 1. Lastly, one of ordinary skill in the art would understand that the ring-opening reaction of the amine with the lactone actually shown original Scheme 1 would not produce a straight-chained sugar residue in the product, but rather an amide having a completely different structure having a cylic sugar residue attached thereto.

Accordingly, Applicants request correction of Scheme 1 to correctly illustrate the structure of the dopamine gluconamide product as possessing a correct 6-carbon sugar residue, rather than an obviously incorrect 7 carbon sugar residue. These corrections are consistent with the text of Example 1.

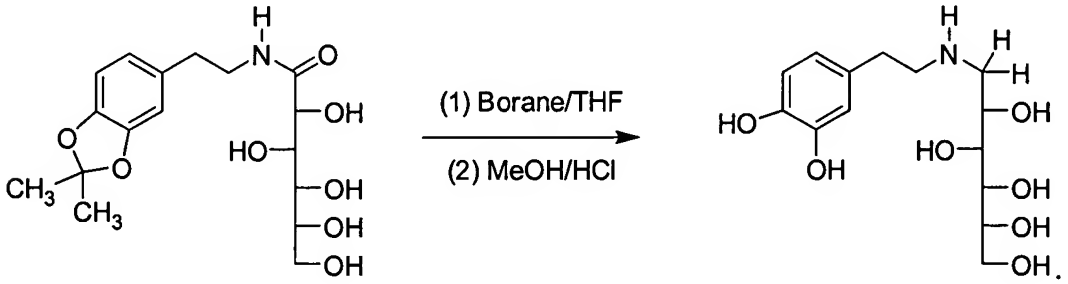


The same erroneous inclusion of an extra 7th carbon atom in the straight chained sugar residues propagated through to Scheme 2 on page 46 and to Scheme 3 on page 47. Accordingly, applicants also submit herewith corrections to Schemes 2 and 3 to correct those original drawings to be consistent with the text of Examples 2 and 3, and the expectations of one of ordinary skill in the art. As such, Scheme 2 has been amended herein to disclose:



Support for this amendment can be found, *inter alia*, in Example 2.

Likewise, Scheme 3 has been amended herein to disclose:



Support for this amendment can be found, *inter alia*, in Example 3.

In addition to support indicated above, support for the amendments can be found throughout the specification and in the claims as originally filed.

Claim Amendments

Claim 1 has been amended to recite that

"Ring 1 has 4 to 8 carbon atoms" and that "X, when present is a carbon atom, $-C(R_1)_2-$ or $-(CR_1)_2-$" and that "Y, when present, is a carbon atom, $-CH_2-$ or CH_2-CH_2-" and that "R_0 is hydrogen." One of skill in the art of organic chemical synthesis would readily understand that

"either -$C(R_1)_2$- or -$C(R_1)_2$-" was an inadvertent redundancy and that "-$(CR_1)_2$-" (*i.e.*, -$C(R_1)$-$C(R_1)$-) was instead meant. To the extent that explicit support is required for these amendments, support can be found at, for example, pages 15-21. No new matter has been added by these amendments.

Claims 2, 4, 7, 9, 11-26, 28-29, and 32 have been amended to correct certain typographical, punctuation, grammatical, and antecedency errors. No new matter has been added by these amendments.

In addition to support indicated above, support for the amendments can be found throughout the specification and in the claims as originally filed.

As discussed in a teleconference with the Examiner, applicant wishes to add new claims 39-75 and to elect prosecution of these new claims. The Examiner indicated in the teleconference that she was not opposed to the addition of a new restriction group which would be elected by applicants. Accordingly, new claims 39-75 have been added herein. No new matter has been added by the new claims. Support for the new claims can be found throughout the specification, as originally filed, and specifically at, for example, pages 15-21 and 46-49.

Restriction Requirement

The Office Action imposed a restriction requirement that restricted the claims into four groups, as recited below:

I. Claims 1-30, drawn to dopaminergic prodrug compounds and compositions thereof, classified in class 536, various subclasses;

II. Claim 31, drawn to a method of treating a dopaminergic transcription regulatory defect, classified in class 514, various subclasses;

III. Claims 32-37, drawn to an assay for identifying candidate drug substances, classified in class 435, subclass 18; and

IV. Claim 38, drawn to a method of treating a tyrosine hydrolase genetic defect, classified in class 514, various subclasses.

Applicants propose the classification of new claims 39-75 into Groups V and VI, as set forth below:

V. Claims 39-62, drawn to compounds comprising an aryl moiety and a residue of a sugar and compositions thereof and methods of making and using same, and

VI. Claims 63-75, drawn to a process for preparing a dopamine amide or a dopamine amine and products thereof.

Applicants provisionally elect Group V, claims 39-62 (or at least the Group classified by the Examiner that contains claim 39), without conceding that the Groups are directed to separate inventions.

In the event that the Examiner declines to modify the restriction requirement, Applicants provisionally elect Group I, claims 1-30, with traverse. Furthermore, Applicants request that the restriction requirement be reconsidered because the Office Action has not shown that a serious burden would be required to examine all the claims. M.P.E.P § 803 provides:

> If the search and examination of an application can be made without serious burden, the Examiner *must* examine it on the merits, even though it includes claims to distinct or independent inventions. (*Emphasis added*)

Thus, for a restriction to be proper, the Office Action must satisfy the following two criteria: (1) the existence of independent and distinct inventions (35 U.S.C. § 121); and (2) that the search and examination of the entire application cannot be made without serious burden. *See* M.P.E.P § 803.

The Office Action has not shown that the second requirement has been met. Specifically, the Office Action has not shown that it would be a serious burden to search and examine all of the groups together. Indeed, the Office Action has not even alleged that it would be a serious

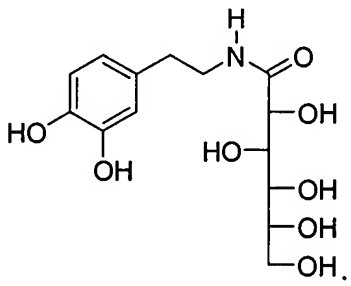
burden to search and examine all of the groups together. Consequently, reconsideration and modification or withdrawal of the restriction is requested.

Election of Species

The Office Action alleges that claims 1-30 are generic to patentably distinct species with no searchable common core and requires election of a single disclosed species.

As stated above, applicants have provisionally elected Group V, claims 39-62, without conceding that the Groups are directed to separate inventions. Applicants assert that Group V does not require election of a single disclosed species.

In the event that the Examiner declines to modify the restriction requirement and that Applicants provisionally elect Group I (claims 1-30) with traverse, Applicants further provisionally elect the disclosed species shown below for examination, with traverse:



Presently, of Group I (claims 1-30), claims 1-4, 6-7, 11, and 21-30 read on the elected species. In the event that the Examiner requires election of a single disclosed species for Group V (new claims 39-62), claims 39-40, 42-44, 46-49, 52, and 55-56 presently read on the elected species.

Applicants note that, upon allowance of a generic claim, Applicants will be entitled to consideration of additional species that are written in dependent form or otherwise include all limitations of an allowed generic claim, as provided by 37 C.F.R. 1.141.

CONCLUSION

Applicants await an action on the merits.

A one-month statutory period was set for response nominally ending July 5, 2006. Also enclosed herewith is a Request for Two-Month Extension of Time, which extends the due date to September 5, 2006. Therefore, this paper is timely.

Payment in the amount of $1850.00 [reflecting a $1625.00 fee for the 37 new claims ($700.00 for 7 new independent claims and $925.00 for the 37 total new claims in excess of twenty) for a small entity and $225.00 for the Two-Month Extension of Time for a small entity] is enclosed herewith. The payment is to be charged to a credit card and is authorized by the signed, enclosed document entitled: Credit Card Payment Form PTO-2038. No further fee is believed due. However, the Commissioner is hereby authorized to charge any fees that may be required or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,
NEEDLE & ROSENBERG, P.C.

D. Brian Shortell, JD, PhD
Registration No. 56,020

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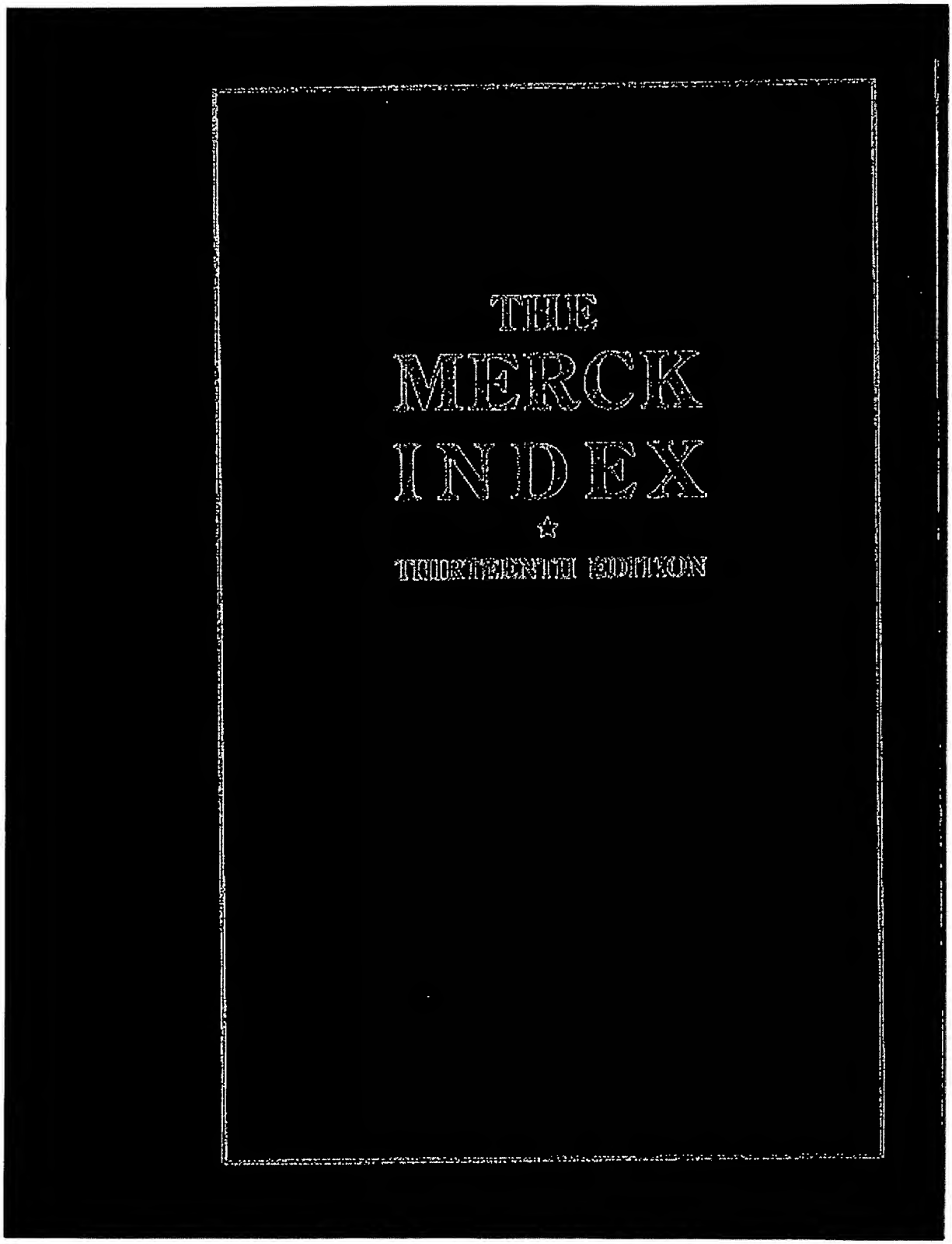
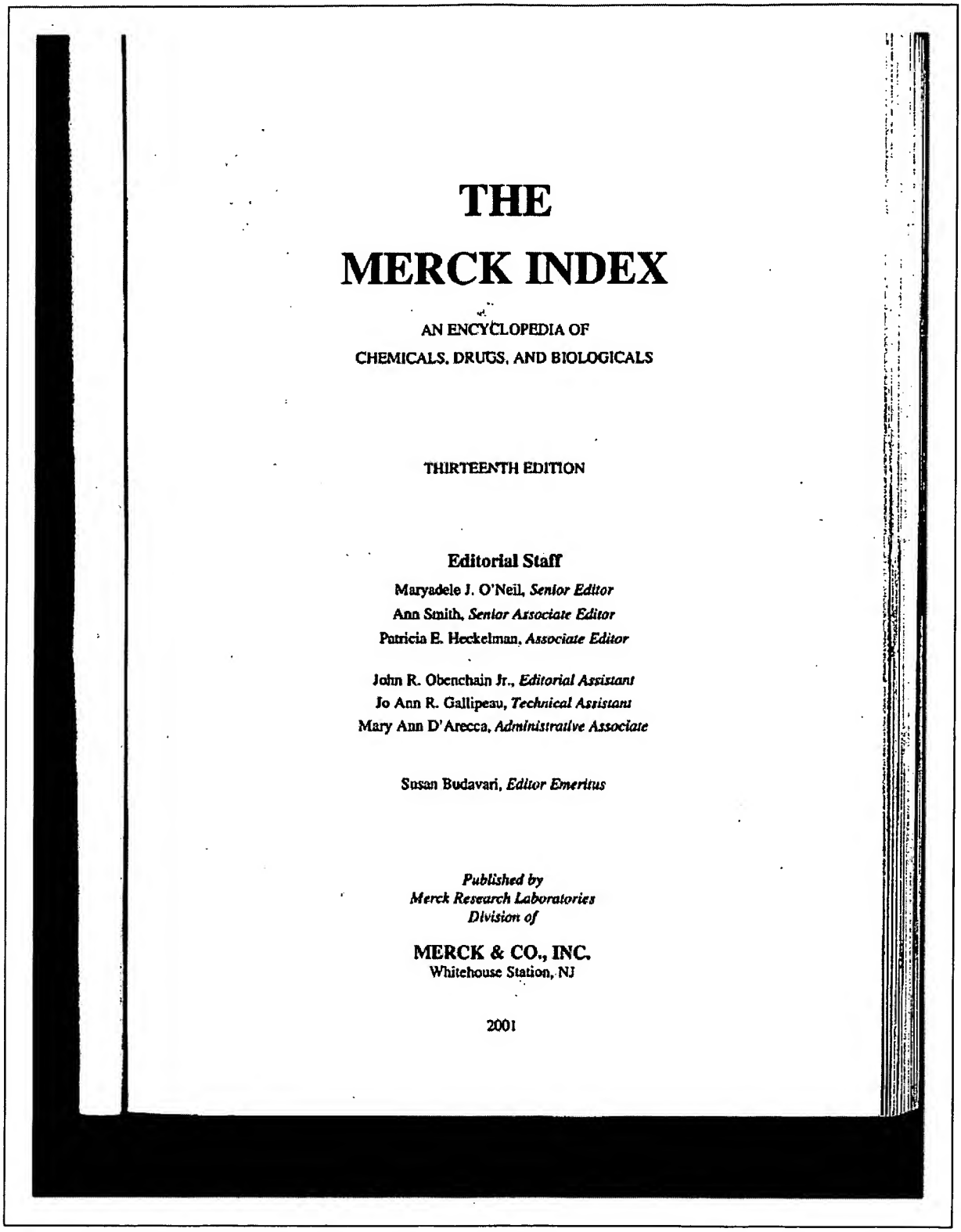
I hereby certify that this correspondence, including any items indicated as attached or included, is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the date indicated below.

D. Brian Shortell, JD, PhD — Date: 18 August 2006

EXHIBIT A





THE

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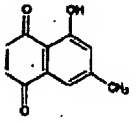
Becomes anhydr at 70° under
$[\alpha]_D^{20}$ −14° (c = 1 as hydrate;
methanol); $[\alpha]_D^{4.5}$ −37.5° (c =
0° (c = 0.75 neutralized with
lubable in water; moderately sol

2731-38-1] Eubalax-N; Ingalu.
56.05%, H 5.23%, O 38.72%.
bark of *Rhamnus frangula* L.
Casparis, Maeder, *Helv. Soc.*
co, Jarpo, *Pharmazie* 14, 316
(1964); *C.A.* 61, 4159h (1964).
rangulin A and glucofrangulin
o the sugar moiety at the 3 po
: Schindler, *Helv. Chim. Acta*
al., *Naturwiss.* 51, 310 (1964);
248 (1964); Wagner, Hörhan-
. Proof of structure of gluco-
: *eidem*, *Z. Naturforsch. B* 24,

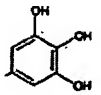


anglin A

3-9] 3-[(6-Deoxy-α-L-manno
nosyloxy)-8-hydroxy-6-meth-

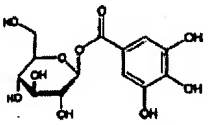
a. $C_{15}H_{10}O_{21}$. Needles from
124° (c = 1.16 in acetone); α
57, 4.56, 4.26).

18-36-8] α-D-Glucopyranose
>-glucopyranose-1-gallate; I
mol wt 332.26. C 46.99%, H
chmidt, Herok, *Ann.* 587, 63
649, 149 (1961).



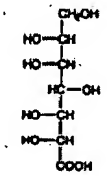
83° (c = 3 in methanol).
, mp 171-173°. $[\alpha]_D^{20}$ +79.8°
anol, ethanol, dioxane, acetic
xetane, ether and acetone.

3-60-2] β-D-Glucopyranose
6-D-glucopyranose-1-gallate;
lucose. $C_{13}H_{16}O_{10}$; mol wt
8.15%. Glucoside of gluco-
eum officinale, Baill., *Poly-*
186, 385 (1903). Structure
on, *Ber.* 51, 1760 (1918);
(1961).



Biner microscopic prisms from water, methanol or 80% ethanol, mp 207°. $[\alpha]_D^{20}$ −24.5° (c = 1.75 in water). Freely sol in hot water. Sparingly sol in cold water, methanol, ethanol, acetone, ethyl acetate. Practically insol in ether, benzene, chloroform, petr ether.

4468. Glucoheptonic Acid. [87-74-1] D-*glycero*-D-*gulo*-Heptonic acid; α-glucoheptonic acid; glucosemonocarboxylic acid; glucomonocarbonic acid. $C_7H_{14}O_8$; mol wt 226.18. C 37.17%, H 6.24%, O 56.59%. Obtained by treating glucose with HCN yielding a cyanohydrin which is saponified to glucoheptonic acid: Kiliani, *Ber.* 19, 769 (1886); Fischer, *Ann.* 270, 71 (1892); Armestar, *C.A.* 45, 2863 (1951). Process starting with calcium cyanide and glucose: Clevenot, US 2735866 (1956 to Lab. Clevenot). Diagnostic use of ^{99m}Tc complexes in renal scintigraphy: R. E. Boyd *et al.*, *Brit. J. Radiol.* 46, 604 (1973); in brain scanning: J. Léveillé *et al.*, *J. Nucl. Med.* 18, 957 (1977); T. W. Ryerson *et al.*, *Radiology* 127, 429 (1978). Subacute toxicity study: L. Belbeck *et al.*, *Can. J. Comp. Med.* 45, 200 (1981).



Lactonizes upon evapn. The lactone forms large sweetish crystals, mp 145-148°. $[\alpha]_D^{20}$ −56.0° (shows mutarotation). Sol in water.

Sodium salt. [13007-85-7] Gluceptate sodium; sodium glucoheptonate. $C_7H_{13}NaO_8$. Prepn from corn syrup: Behnke, US 3022343 (1962 to Pfanstiehl Labs). Crystals (α-form), dec 161°. $[\alpha]_D^{20}$ +6.06° (c = 10 in H_2O). Freely sol in water.

Calcium salt. Gluceptate calcium; calcium glucoheptonate; calcium glucosemonocarbonate; calcium glucomonocarbonate; Calciforo; CaDepense. $C_{14}H_{26}CaO_{16}$; mol wt 490.42. Prepn from Na salt: Holstein, US 3033900 (1962 to Pfanstiehl Labs.). Hygroscopic crystals, somewhat acrid taste, dec 200°. Sol in water.

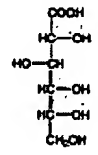
Magnesium salt. Magnesium glucoheptonate; magnesium glucosemonocarbonate; magnesium glucomonocarbonate; Navolin. $C_{14}H_{26}MgO_{16}$; mol wt 474.65. Prepn: Cipelli, US 3043896 (1962 to Merck & Co.). Water-sol crystals, pleasant taste.

Complex with ^{99m}Tc. ^{99m}Tc gluceptate; ^{99m}Tc glubeptonate; Glucoscan; TechneScan gluceptate.

USE: Pharmaceutic aid.

THERAP CAT: ^{99m}Tc complex as diagnostic aid (radioactive imaging agent).

4469. Gluconic Acid. [526-95-4] D-Gluconic acid; dextronic acid; maltonic acid; glyconic acid; glycogenic acid; pentahydroxycaproic acid. $C_6H_{12}O_7$; mol wt 196.15. C 36.74%, H 6.17%, O 57.10%. Prepd by oxidation of glucose: H. Hlasiwetz, J. Habermann, *Ann.* 155, 120 (1870); J. Habermann, *Ibid.* 162, 297 (1872). Fermentative prepn using *Aspergillus niger*: K. Bernhauer, L. Scholof, US 1869053 (1932 to Pfizer); A. J. Moyer *et al.*, *Ind. Eng. Chem.* 32, 1379 (1940). Review of preps and uses: P. J. Prescott *et al.*, *Ibid.* 45, 338 (1953); M. Roehr *et al.*, in *Biotechnology*, Vol. 6, H. Rehm, G. Reed, Eds. (VCH, Weinheim, 2nd ed, 1996) pp 347-362. *See also* Gluconolactone.



Crystals, mp 131°. Mild acid taste. $[\alpha]_D^{20}$ −6.7° (c = 1). pK (25°) 3.60. Freely sol in water, slightly sol in alcohol. Insol in ether and most other organic solvents. In aq solns the acid is partially transformed into an equilibrium mixt with gamma and delta gluconolactones.

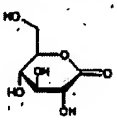
Magnesium salt. [3632-91-5] Magnesium gluconate; Almore; Ultra-Mg. $C_{12}H_{22}MgO_{14}$; mol wt 414.60. Clinical pharmacokinetics and use as magnesium supplement: J. White *et al.*, *Clin. Ther.* 14, 678 (1992). Also occurs as the dihydrate. Sol in water, slightly sol in alcohol. Insol in ether.

Zinc complex. [4468-02-4] (*T*-4)-Bis-(D-gluconato-κO^1,κO^2)zinc; zinc gluconate; Ribozinc. $C_{12}H_{22}O_{14}Zn$; mol wt 455.73. Review of clinical use in treatment of colds: M. L. Garland, K. O. Hagmayer, *Ann. Pharmacother.* 32, 63-69 (1998). Clinical trial in inflammatory acne: J. Meynadier, *Eur. J. Dermatol.* 10, 269 (2000).

USE: Chelating agent. In high alkalinity bottle washes and other cleansers; in finish removers; in the tanning and textile industry.

THERAP CAT: Magnesium salt as magnesium replenisher; zinc complex as zinc supplement.

4470. Gluconolactone. [90-80-2] D-Gluconic acid δ-lactone; glucono delta-lactone; delta gluconolactone; Fujiglucon. $C_6H_{10}O_6$; mol wt 178.14. C 40.45%, H 5.66%, O 53.89%. Prepn by oxidation of glucose with bromine water: Isbell, Pigman, *J. Res. Nat. Bur. Stand.* 10, 337 (1933); by oxidation of glucose in *Acetobacter suboxydans*: King, Cheldelin, *Biochem. J.* 68, 31P (1958). Structure: J. Sinnék *et al.*; *The Monosaccharides* (Academic Press, New York, 1963) p 271.



Crystals, dec 153°. Sweet taste (different from gluconic acid). $[\alpha]_D^{20}$ +61.7° (c = 1). Soly in water 59 g/100 ml; in alc about 1 g/100 g. Insol in ether. Hydrolyzed to gluconic acid by water. A freshly prepd 1% aq soln has a pH of 3.6 changing to pH 2.5 within 2 hrs.

USE: Component of many cleaning cmpds because of the sequestering ability of the gluconate radical which remains active in alk solns; in the dairy industry to prevent milkstone; in breweries to prevent beerstone; as latent acid catalyst for acid colloid resins, particularly in textile printing; as a coagulant for tofu.

4471. Glucosamine. [3416-24-8] 2-Amino-2-deoxy-D-glucose; chitosamine. $C_6H_{13}NO_5$; mol wt 179.17. C 40.22%, H 7.31%, N 7.82%; O 44.65%. Found in chitin, in mucoproteins, and in mucopolysaccharides. Isols from chitin: Ledderhose, *Z. Physiol. Chem.* 2, 213 (1878); Hackman, *Aust. J. Biol. Sci.* 7, 168 (1954). Synthesis: Fischer, Leuchs, *Ber.* 35, 3787 (1902); 36, 24 (1903); Separation of α- and β-forms: Westphal, Holzmann, *Ibid.* 75B, 1274 (1942). Structure: Haworth *et al.*, *J. Chem. Soc.* 1939, 271; Cutler, Peat, *Ibid.* 782; Cox, Jeffrey, *Nature* 143, 894 (1939). Pharmacokinetics in dog and man: I.